C. Remarks

The claims are 56-58, 60, 64, 66-68 and 74-83, with claims 74 and 83 being independent. New claim 83 has been added to give Applicant a more complete scope of protection for the invention. The new claim is fully supported by the application as originally filed, and none of the prior art of record discloses the simple use of activated charcoal to remove tin from a polylactide polymer. Reconsideration of the pending claims is respectfully requested.

Claims 55, 56, 58, 60, 64, 66-68 and 74-82 stand rejected under 35 U.S.C. §103(a) as being obvious over Bodmer (U.S. Patent No. 5,538,739) in view of GB 2,145,422 (Brich) and Reiners (U.S. Patent No. 4,879,402). Applicant respectfully traverses this rejection.

At the outset, Applicant incorporates by reference herein the arguments advanced in previous responses. In particular, Applicant would like to draw the Examiner's attention to the Declaration under 37 C.F.R. §1.132 of Martin Schneider, which states, in pertinent part:

> One of ordinary skill in the art would not recognize that activated charcoal will bind the octoate chain, removing the tin counterion as well. In fact, purification does not proceed in the manner proposed in the Office Action. In practice, the activated charcoal will remove the tin metal ion, but a second purification step is required to remove the ethyl hexanoate acidic group which remains after the tin metal ion removal. Hence, even if one of ordinary skill in the art were to combine Reiners with Bodmer and GB '422, at least the ethyl hexanoate impurity would remain in the polymer.

In the outstanding Office Action, the Examiner alleges that, contrary to Mr. Schneider's previously filed declaration, charcoal is used to remove organic impurities because it is a carbonaceous material and that "it is the octoate which binds to charcoal". It remains Applicant's position that the Examiner is incorrect on these points.

In obtaining the pharmaceutical composition of the present invention, charcoal treatment is not used to remove the color of tin octoate, as tin octoate is slightly yellow to colorless, while the crude polymer is dark brown. Furthermore, Applicant again submits that the charcoal treatment removes tin, but not the octoate as set forth in Mr. Schneider's declaration. (Incidentally Applicant has added a claim directed generally to a method of removing tin from a polymer using charcoal treatment.) In response to the Examiner's contradiction of the statements made in Mr. Schneider's declaration, Applicant submits herewith the translation of a technical report from Ciba Expert Services where the polymer was investigated thoroughly after charcoal treatment. As can be seen at page 6 of the report, all sample fractions had considerable amounts of ethyl-2-hexanoate whereas, as can be seen at page 9, the tin content of those same samples had been lowered by a factor of 100 to 1000 after charcoal treatment. These results would appear to support the notions that the adsorption of organic molecules to charcoal is selective, that perhaps the tin is somehow complexed with polymer molecules, and that perhaps those larger organic molecules are preferably adsorbed by the charcoal as compared to the smaller octoate molecules.

In any event, one of ordinary skill in the art would not arrive at the pharmaceutical composition of the present invention given the combined disclosure of Bodmer, Brich and Reiners at least since the octanoate would remain in any polymer treated in accordance with the combined prior art. Accordingly, Applicant respectfully requests withdrawal of the §103 rejection.

This Amendment After Final Rejection is believed clearly to place this application in condition for allowance; at the very least, it simplifies the issues for appeal. Its consideration is therefore believed proper under 37 C.F.R. §1.116. Accordingly, entry of this Amendment After Final Rejection, as an earnest attempt to advance prosecution, is respectfully requested. Should the Examiner believe that issues remain outstanding, the Examiner is respectfully requested to contact Applicants' undersigned attorney in an effort to resolve such issues and advance the case to issue.

Applicant's undersigned attorney may be reached in our New York office by telephone at (212) 218-2100 or at the below listed address. All correspondence should continue to be directed to Novartis, Corporate Intellectual Property, One Health Plaza 104/3, East Hanover, NJ 07936-1080.

Respectfully submitted,

/Elizabeth F. Holowacz/
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Attorney for Applicant
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[Translation from German]

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Preparative GPC Separation of Two D,L-PLGGLU Batches with Subsequent Analytical Testing

Request Nr.: CXS06.0524 Modul 3a PN228090603	Customer: Novartis Pharma AG Herrn Dr. K. Büscher WSJ-145.10.53, CH-4002 Basel
☒ Analytical Testing ☐ Performance Testing ☐ Method Development ☐ Training ☐ Others	Sample(s) provided by: ☒ Customer ☐ In-house ☐ Third party
Lab.: K-402.3.36	Date: 08.01.2007

Introduction:

Preparative GPC separation of each of two batches of PLGGLU, "Batch C0129" and "Batch C0129 Reproc.," into 4 fractions (low-molecular, two medium fractions and one high-molecular fraction) with subsequent analysis by NMR, GPC with calculation of the branching factor, determination of Sn content and mass spectrometry of the low-molecular fractions.

Release of the four preparatively isolated fractions per batch to Customer for further use.

GPC Method for Preparative Separation:

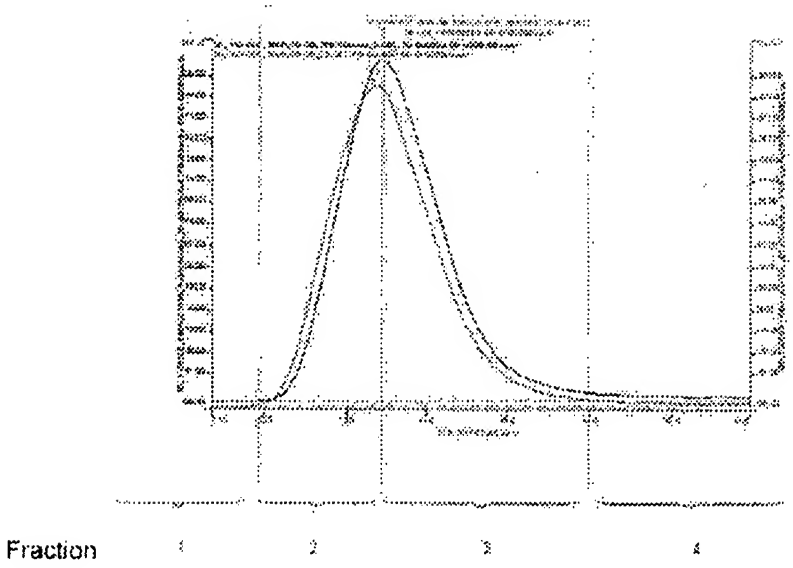
The preparative separations with GPC were carried out at room temperature using a PL_{Gel} multicolumn combination covering a wide range of molecular weights with THF as solvent and RI detection.

Analytical Methods:

- **SEC** coupled with **RI, RALS, LALS and DP (viscosity) detection** for the determination of molecular weight by relative (narrowly distributed polystyrenes) and absolute calibration, as well as of the degree of branching on the basis of Mark-Houwink parameters a and K.
- **^{1}H, ^{13}C and 2D NMR measurements.**
- **ESI-TOF**
- **Sn-content determination** by means of ICP/AES

Results of GPC Separation:

The two PLGGLU **batches C0129** and **C0129 reproc.** were each separated into 4 fractions. The main peak was separated into two fractions (Fractions 2 and 3), and Fractions 1 and 4 were collected before and after the main peak (see example chromatogram below).



Mass balance

Fraction	Batch C0129	Batch C0129 reproc.
1	10 mg	70 mg
2	1470 mg	900 mg
3	2340 mg	560 mg
4	40 mg	230 mg

The amounts of preparatively isolated fractions indicated above may be released to the Customer.

Results of GPC Testing:

- Molecular weight parameters and data for branching analysis at an average molecular weight M_w are summarized in Tables 1 and 2.
- The GPC chromatogram (see Figures 1 and 2) and also the table values for the fractions of PLGGLU **"Batch C0129"** and PLGGLU **"Batch C0129 Reproc."** show clearly that a separation into a variety of molecular weight ranges took place.

- As already established for the total amount (see Report of 17 October 2006), the fact that significantly lower molecular weights are to be found for **"Batch C0129 Reproc."** as a whole, as well as for the individual fractions, than for **"Batch C0129"** is confirmed anew.
- The highest molecular portion over 80,000 Da (Fraction 1 from **"Batch C0129"**) in particular is missing in **"Batch C0129 Reproc."**
- While, as to be expected, the two middle main fractions for **"Batch C0129 Reproc."** differ only by a different molecular weight, in the case of the two corresponding fractions for **"Batch C0129"** for the higher molecular fraction, in addition to higher molecular weight, a distinctly higher branching factor is also to be found. This value, derived from the intrinsic viscosity, proves that this fraction is clearly more compact than the other fractions.

Table 1: Molecular weight parameters (M_n, M_w, M_w/M_n) and branching at M_w of D,L-PLGGLU "Batch C0129" and its preparative fractions from GPC

Sample	Polystyrene calibration			Absolute calibration	
PLGGLU	M_n	M_w	M_w/M_n	M_w	Branching at Mw f_{η}
Batch C0129	18'300	52'600	2.7	58'600	2.2
Fraktion 1[1]	-	>150'000[2]	-	-	-
Fraktion 2	61'500	83'100	1.4	96'200	0.6
Fraktion 3	24'100	48'500	2.0	38'800	3.9
Fraktion 4[1]	500	6'300	13.0	-	-

[1] Exact weighed portions of these fractions were not possible, since the components contained therein either settled on the wall of the flask as a fine "oily film" or the amounts of material required for a useful weighed portion were simply too small. Hence, only a relative molecular weight determination was possible.

[2] Exclusion limit of the two-column combination: about 150,000 Da.

Table 2: Molecular weight parameters (M_n, M_w, M_w/M_n) and branching at M_w of D,L-PLGGLU "Batch C0129 Reproc" and its preparative fractions from GPC

Sample	Polystyrene calibration			Absolute calibration	
PLGGLU	M_n	M_w	M_w/M_n	M_w	Branching at Mw λ_w
Batch C0129 Reproc.	17'300	46'100	2.7	46'800	2.0
Fraktion 1	62'700	84'500	1.4	-	-
Fraktion 2	41'600	58'400	1.4	45'900	2.9
Fraktion 3	24'300	41'700	1.7	30'600	3.0
Fraktion 4	1'800	19'700	10.9	-	-

Results of NMR Testing:

- When the ^1H NMR spectra of the two total batches are considered, they are largely identical. The ^{13}C NMR spectra are fingerprint identical.

- The NMR spectra of the individual fractions show no perceptible difference, with respect to intensities and peak shape, for PLGGLU peaks, in either the ^1H or the ^{13}C NMR.

- In each of the two middle fractions (2 and 3), the spectra contain substantially only the sets of peaks to be expected for PLGGLU.

- In all fractions residual THF or 4 hydroxybutanal and derivatives thereof are still to be observed as oxidation products of THF. The latter show up more distinctly especially for Fractions 1 and 4, since these are quantitatively substantially smaller than the middle fractions.

- Despite this, it was attempted to obtain as many data as possible from the NMR spectra. The results are summarized in Table 3.

When the results are again considered first for the total batches:

- It is striking that the glycolide portion falls after reprocess and the portion of free lactide increases. This latter observation was already made analogously in the tests concerning the various processing steps.

- The ethyl-2-hexanoate (oct) portion from tin octoate apparently increases slightly.

However, this may also be due to the inaccuracy (peak superposition) of integration.

Table 3: Selected NMR spectroscopic data

D,L – PLGGLU	I(3.8 ppm)*	DR from NMR	mol% glycolide (G+L=100%)	Monom. lactide+ (G+L=100%)	Ethyl-2-hexanoate (G+L=100%)
Batch C0129	0.052	2.5	45.1%	0.2%	0.036%
Fraction 1 Batch C0129	++		46.3%	n.d.	++
Fraction 2 Batch C0129	++		45.2%	n.d.	0.018%
Fraction 3 Batch C0129	++		45.1%	n.d.	0.024%
Fraction 4 Batch C0129	++		45.9%	1.4%	++

D,L – PLGGLU	I(3.8 ppm)*	DR from NMR	mol% glycolide (G+L=100%)	Monom. lactide+ (G+L=100%)	Ethyl-2-hexanoate (G+L=100%)
Batch C0129 Reproc.	0.068	3.5	43.8%	0.4%	0.056%
Fraction 1 Batch C0129 Reproc.	++		42.7%	n.d.	++
Fraction 2 Batch C0129 Reproc.	++		44.3%	n.d.	0.016%
Fraction 3 Batch C0129 Reproc.	++		44.0%	n.d.	0.027%
Fraction 4 Batch C0129 Reproc.	++		44.3%	0.4%	0.209%

* From ^{1}H NMR; I(CH_2–glycolide) = 200
+ mol% of lactide subunit referred to G+L=100%
++ Values not identifiable because of peak superposition.
n.d. Not detectable.

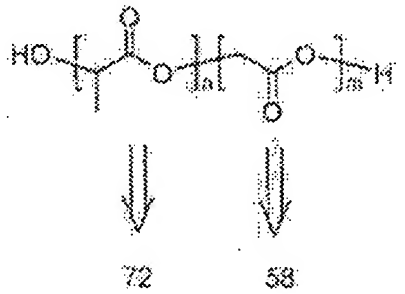
Consideration of individual fractions:

- The glycolide portion is the same over the individual fractions within the limits of error.
- As to be expected, free lactide is in each case found only in Fraction 4, which of course must contain the low-molecular portion. Free lactide is not detectable in the other fractions.
- The corresponding situation is also observed for ethyl-2-hexanoate. The portion is distinctly higher in Fraction 4 in each instance, although a significant portion is still detectable in Fractions 2 and 3.
  Here, ethyl-2-hexanoate possibly is present bound to or coordinated with PLGGLU, which could explain eluation with the high molecular portions.
  Whether the portion of ethyl-2-hexanoate (oct) is present coordinated with tin or is free cannot be decided by these NMR experiments.

Results of MS Tests:

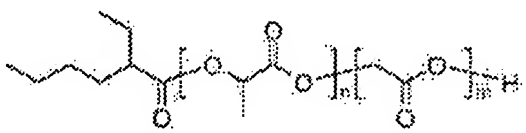
The low molecular Fractions 4 of both batches were tested by ESI-MS. There a variety of distributions with a mass difference of 14 were found (Figs. 3 and 4). This difference corresponds to the difference of the monomer unit (72), and glycolide (58).

The distributions found do not match an H_2O-terminated polylactide glycolide.



H_2O-terminated polylactide glycolide

What would match much better is a polymer that bears a C8 acid as starter. The origin of the acid could be the dioctyl-tin catalyst used in polymerization.



Polylactide glycolide started with octanoate

Among others, the following distributions were found:

m/z 399 + a *14 (a = 0 -- 4)
m/z 457 + a *14 (a = 0 – 5)
m/z 515 + a *14 (a = 0 –6)

These match the following polylactide glycolides started with octanoate:

m/z [M+Na]+	Number of glycolide units	Number of lactide units
399	4	0
413	3	1
427	2	2
441	1	3
455	0	4
457	5	0
471	4	1
485	3	2
499	2	3
513	1	4
527	0	5
515	6	0
529	5	1
543	4	2
557	3	3
571	2	4
585	1	5
599	0	6

Results of Sn Determinations:

Fraction	Sn content (Batch C0128)	Sn content (Batch C0129 reproc)
1	*	*
2	< 10 mg/kg	< 10 mg/kg
3	< 10 mg/kg	50 mg/kg**
4	*	*
tel quel	2 mg/kg+	< 1 mg/kg

* Not determined.

** This value is very likely an outlier or a measurement error. Because of the small sample amounts, however, only single determinations could be carried out, and hence clarification of the situation was not possible. This measured value is therefore not taken into consideration in the further discussion.

\+ 2 mg/kg corresponds to about 0.00011 mol% referred to one lactide/glycolide subunit (100%).

No definite statement as to how the tin is distributed in the individual fractions can be made. Because of the small sample amounts and the low contents of tin, the test results do not provide enough worthwhile information.

When the tin content is compared with the ethyl-2-hexanoate content, it is striking that there is no correlation. In each instance, the tin content lies below the ethyl-2-hexanoate content by a factor of at least 100 to 1000.

Discussion and Summary:

The two batches were each separated into four fractions by means of preparative GPC. Clear differences in the molecular weight profile between the two batches were worked out by subsequent characterization by means of analytical GPC.

It was shown by NMR spectroscopy that the glycolide/lactide ratio remains constant in all 4 fractions. An elevated portion of octanoate was found in the lowest molecular Fraction 4.

ESI-MS tests with Fraction 4 confirm the elevated octanoate portion (octanoate-started polylactide glyocolide).

When Fraction 3 of "Batch C0129 Reproc." with a content of 0.027 mol% octanoate referred to a glycolide/lactide subunit is considered, the portion referred to a macromolecule amounts to only 12%. i.e., of the PLGGLU originally started with octanoate, only a small portion (12%) can still be present chemically bound with the octanoate. The percentage may be greater in Fractions 4, but in every case unbound octanoate also elutes in these fractions.

Albert Horni
Structure Elucidation
Expert Services

Dr. Gerd Scherer
Structure Elucidation
Expert Services

Appendix:

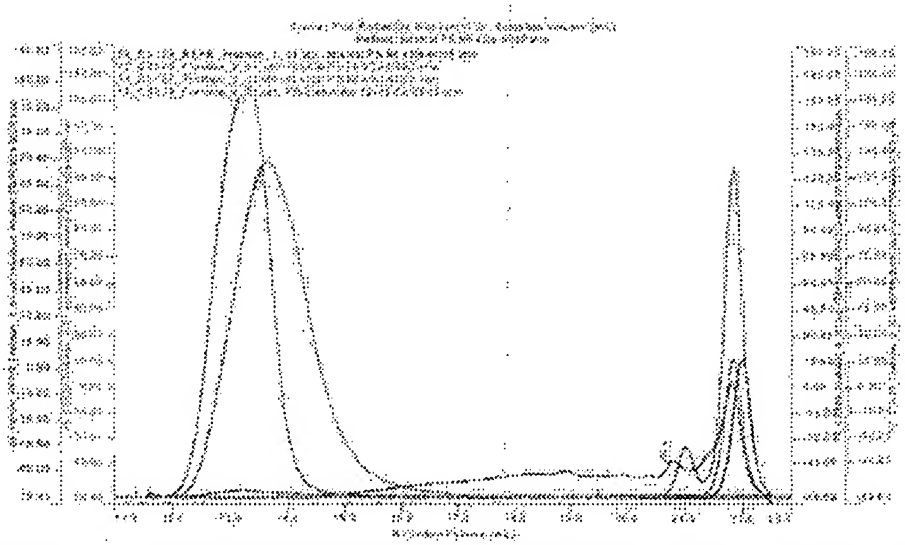


Figure 1: Overlap of analytical GPC chromatogram of Fraction 1 (black), Fraction 2 (green), Fraction 3 (red) and Fraction 4 (blue) in preparative GPC of D,L-PLGGLU Batch C0129.[3]

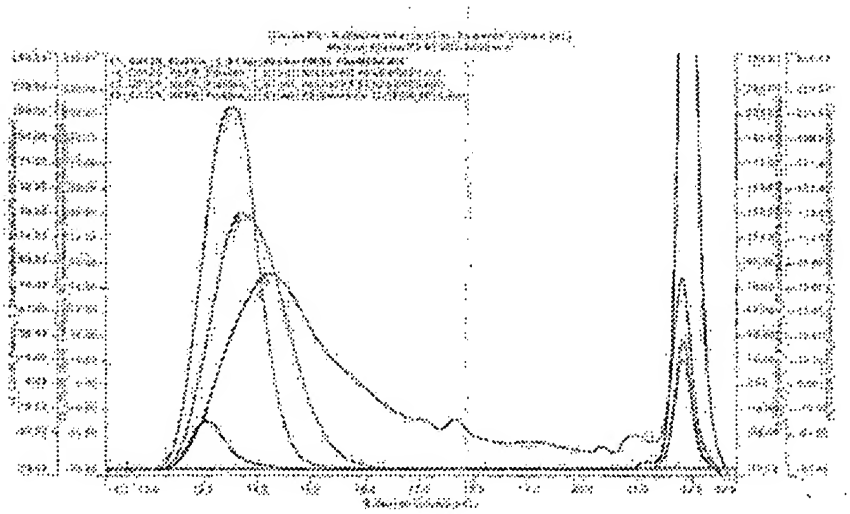


Figure 2: Overlap of analytical GPC chromatogram of Fraction 1 (black), Fraction 2 (green), Fraction 3 (red) and Fraction 4 (blue) in preparative GPC of D,L-PLGGLU Batch C0129 Reproc.[3]

[3] Peaks above 20.5 ml retention volume are system peaks.